Malabsorption

Introduction

This lesson is titled *Malabsorption*. However, if macronutrients aren't first digested to small polymers, or if small polymers cannot be digested into their monomers, absorption cannot occur. Thus, we start this lesson by discussing malabsorption mechanisms, which, as you will see, tend to be more related to digestion than absorption. Both the inability to digest and the inability to absorb are considered malabsorption syndromes.

We'll then go into detail on a few diseases. First, the presentation of fat malabsorption due to impaired digestion—pancreatic insufficiency and bile salt deficiency. Then, we'll transition to a smattering of diseases with variable pathology. There will be a strong emphasis on celiac disease and gluten insensitivity, a brief mention of issues of terminal digestion—lactose intolerance—and we'll close with two of the other commonly tested pathologies: environmental enteropathy (tropical sprue) and Whipple's disease.

Malabsorption Mechanisms

Malabsorption results from a failure of at least one of the four phases of nutrient absorption: intraluminal digestion, terminal digestion, transepithelial transport, or lymphatic transport.

Problems with **intraluminal digestion** are synonymous with biliary tree secretion deficiencies. The digestive enzymes come from the pancreas. Bile acids come from the gallbladder. So "intraluminal digestion" really means, "the enterocytes are totally intact; it's other organs not doing their job." Pancreatic insufficiency is the key diagnosis. Problems with **terminal digestion** are enterocyte problems. The pancreas and gallbladder did their job; the big molecules got chewed up to smaller ones. Not small enough to be absorbed by enterocytes, but small enough for the brush border enzymes to finish the job. A failure of terminal digestion must be due to either an injury to the epithelium (such as in celiac disease) or an enzymatic defect (such as lactose intolerance). After terminal digestion, the enterocytes must then absorb the nutrients across their lumen. **Transepithelial transport** is compromised in extremely specific genetic diseases (Hartnup disease, cystinuria) or if the epithelium is injured (again, such as in celiac disease). Finally, the nutrients need to get out of the enterocytes and into the bloodstream. There are no real disorders of getting nutrients into the bloodstream. Lipids, however, go through lacteals. Unique to lipid absorption, **lymphatic transport** may be impaired.

DISEASE	INTRALUMINAL DIGESTION	TERMINAL DIGESTION	TRANSEPITHELIAL TRANSPORT	LYMPHATIC TRANSPORT
Celiac sprue		+	+	
Environmental enteritis		+	+	
Cystic fibrosis	+			
Chronic pancreatitis	+			
Bile acid malabsorption	+		+	
Whipple's disease (*T. whipplei*)				+
Lactase deficiency		+		
Crohn's disease		+	+	

Table 9.1: Malabsorption Syndromes by Mechanism

This is the reason that licensing exams love the **D-xylose absorption test**. You will likely never actually order this test because the diagnosis is usually obvious given the overarching presentation. However, the D-xylose absorption test is commonly tested on licensing exams because it assesses your understanding of digestion and absorption. An oral dose of D-xylose, a monosaccharide that requires no digestion to be absorbed, is administered. It is readily absorbed by the brush border, circulated in the serum, and eliminated in the urine. If the epithelium is impaired, then no absorption can occur, and no D-xylose will be found in the serum or urine. Repeating the test after administering antibiotics will determine whether there was **bacterial overgrowth** (urine D-xylose returning to expected levels after antibiotics and a subsequent dose of D-xylose) or a **deficiency in the brush border** (indicating celiac disease). If the malabsorption was caused by an enzyme deficiency, whether at the brush border or from the pancreas, D-xylose levels would be normal as it is a monosaccharide and requires no digestion. This test was formerly used to diagnose celiac disease but has been replaced by antibody testing and endoscopy.

Fat Malabsorption Syndromes

Fat malabsorption will result in osmotic diarrhea. If fats cannot be digested or absorbed, they act as an osmolar load, drawing water into the lumen. We will discuss fat malabsorption diarrhea in GI: Digestion and Absorption: Start to Finish #13: *Functional Intestinal Disease*. Here, we'll focus on the cause of fat malabsorption. To be brief, fatty stools are greasy, difficult to flush, and foul-smelling. If fat is lost in the stool, then fat-soluble vitamins (ADEK) are also lost. There is also usually weight loss. For fat digestion and absorption to occur, there must be both **bile salts** to stabilize emulsion droplets and mixed micelles, and **pancreatic lipase**. If either is deficient, fat malabsorption results.

The deficiency of pancreatic lipase is seen in cases of **chronic pancreatitis** and **cystic fibrosis**. Chronic pancreatitis is caused by recurrent bouts of acute pancreatitis (i.e., seen in older patients with such a history). When at the chronic pancreatitis stage, there may also be a concomitant endocrine dysfunction. Abdominal imaging will show calcifications. **Cystic fibrosis** is an inheritable disease—autosomal recessive—that causes a deficiency or loss of the cystic fibrosis transmembrane conductance regulator (CFTR protein encoded by the ***CFTR* gene**). CFTR is a chloride channel and the mechanism by which ductal cells secrete bicarbonate- rich aqueous fluid. So, without the ability to secrete fluid, the patients present with **pancreatic insufficiency**. The CFTR channel is used throughout the body. All exocrine secretory glands use this channel to generate their secretions. In the skin, sweat glands use the channel to draw chloride back into the cytoplasm of ductal cells, where sodium follows to balance the electric gradient, while the epithelium, with strict tight junctions, is completely impermeable to water, including paracellular shifts. Children with cystic fibrosis will have **salty skin** (sodium and chloride are not reabsorbed as they normally would be in the ducts of sweat glands). In the airway, the aqueous environment under the air-surface liquid (mucus) and even the water content of mucus and the pericilliary layer are dependent on CFTR's extrusion of chloride. Patients with cystic fibrosis present with **pulmonary infections** and **thick mucous secretions**. There are multiple mutations and multiple degrees of defect, so we want you to focus on the pancreas presentation because we're here in GI. **No pancreatic enzymes** mean no digestion of proteins or fats, resulting in failure to thrive in some forms of cystic fibrosis, and **short height** in nearly every form. By replacing the pancreatic enzymes (orally with meals), that element of the disease can be alleviated. The point is, without chemical digestion by pancreatic enzymes, proteins and fats cannot be digested and, therefore, cannot be absorbed.

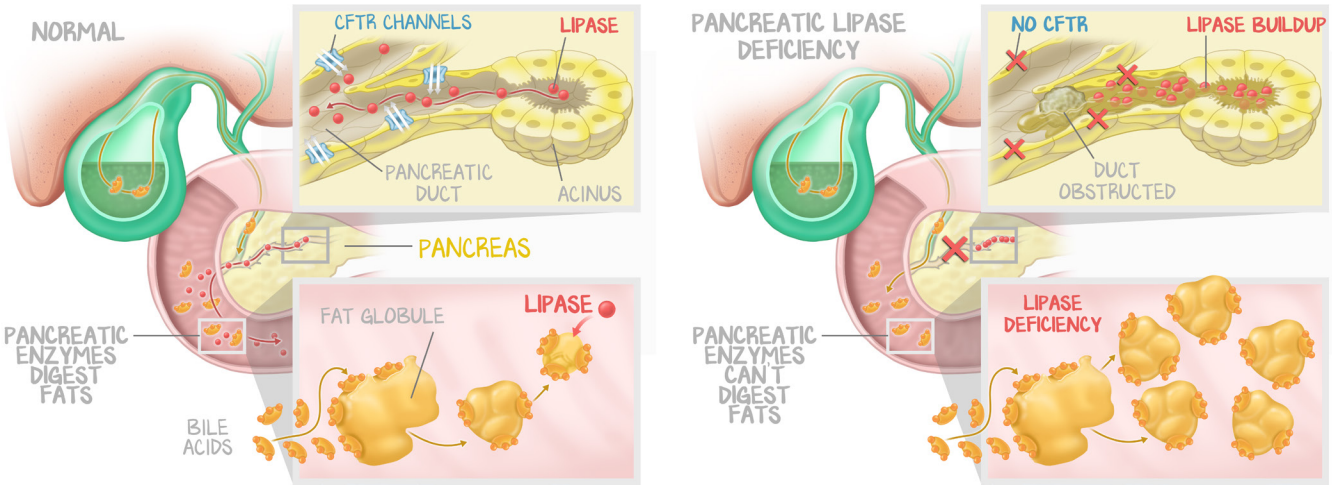

Figure 9.1: Pancreatic Insufficiency Malabsorption
If pancreatic enzymes can't get into the duodenum lumen for any reason—there's a mass preventing it, the chloride channel gene is defective, there aren't any pancreatic cells to make them—pancreatic enzymes can't act on the partially digested food. This results in a deficiency in lipases and proteases, causing severe malabsorption of lipids and protein, respectively.

The deficiency of bile acids is seen in **Crohn's disease** (when Crohn's inflammation affects the terminal ileum) and resection of the **terminal ileum**. Resection of the terminal ileum in Crohn's disease may be required due to disease complications. Any resection of the terminal ileum will impair bile acid reabsorption because bile salts (which are ionized) are actively reabsorbed via bile salt transporters that are only located in the terminal ileum. And although bile salt deficiency isn't as bad as pancreatic insufficiency (because proteins can still be digested and absorbed), losing bile salts means less lipid digestion, leading to fat malabsorption and fat-soluble vitamin (ADEK) deficiencies.

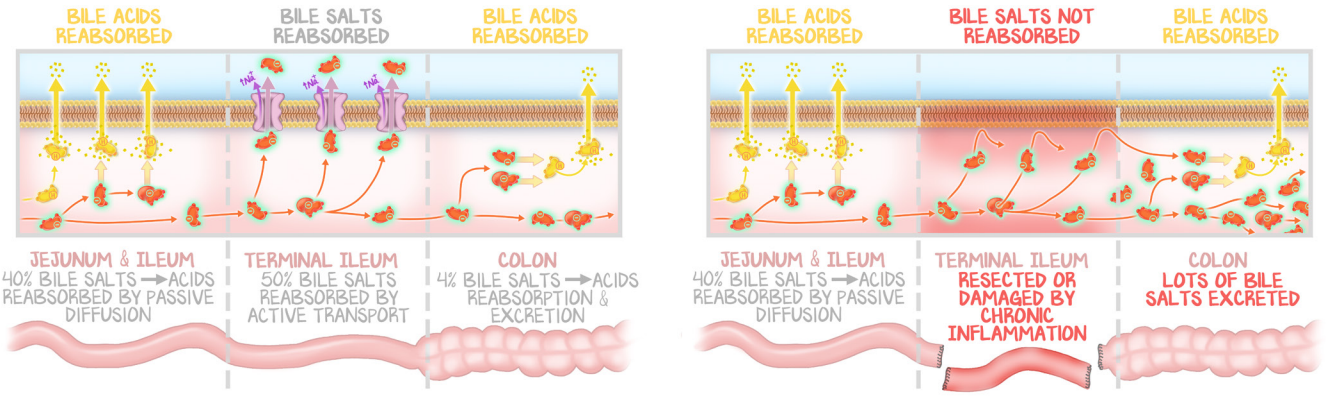

Figure 9.2: Bile Acid Insufficiency
Bile salts are secreted into the lumen to aid the digestions and absorption of lipids. If pancreatic enzymes are present but bile salts are not, the lipases cannot access the lipids as well, so they go undigested and unabsorbed. Every cause of bile salt deficiency results in the same thing—the maldigestion of lipids.

Malabsorption Syndromes #1: Celiac Disease

Celiac disease (also called celiac sprue) is a really easy diagnosis when it comes to clinical science—if a patient eats gluten, they will get diarrhea, EGD will show blunting of intestinal villi, and their blood will be positive for Celiac antibodies. The diagnosis is easy to make (antibodies, biopsy, or positive response to a gluten-free

diet). The diagnosis is easy to treat (avoid gluten). Well, it's easy to treat from the provider's perspective, but not so much from the patient's perspective, as avoidance of gluten every day and forever is not easy.

Celiac sprue is really hard when it comes to the basic sciences, as its mechanism is complex and not fully elucidated. But here is what is known:

First and foremost, celiac disease is NOT a type II cytotoxic hypersensitivity reaction. There are specific antibodies that circulate in almost all patients with celiac disease. They are extremely useful **for the diagnosis** but are unlikely to contribute to the pathogenesis. Despite the presence of IgA and IgG against tissue transglutaminase (anti-tTG), tissue transglutaminase 2 (anti-TG2), and gliadin (anti-gliadin), there is no evidence of acute inflammation (no neutrophils, macrophages, fibroblasts) on intestinal biopsies. Patients who lack IgA still get the disease, and animals immunized to generate anti-tTG and -gliadin antibodies (both IgA and IgG) do not develop the disease when exposed to gluten. The antibodies are ancillary to the pathogenesis of the disease but are a marker of disease activity. Their presence helps identify the diagnosis, and their decrease over time is a marker of disease remission.

What, then, is the pathogenesis? Medical science has not elucidated the entire story, but there has been significant advancement. Because we don't want you bogged down by gene names (which are all unpronounceable acronyms), we're going to say "NKRs" and "NKR ligands." While not all are actually natural killer receptors, it's convenient for us (and pretty close to the truth) to refer to them all as one thing. Intraepithelial $CD8^+$ cytotoxic T lymphocytes (IE-CTLs) can express NKRs when told to do so. The enterocytes of the duodenal epithelium can express NKR ligands when told to do so. If IE-CTLs express NKRs and enterocytes express NKR ligands, the end result is apoptosis of the epithelium. This only happens in genetically susceptible people who have a dysfunctional $CD4^+$ lymphocyte response to gluten antigens (gliadin), and when gluten antigens (gliadin) are present.

On first exposure, a person with a genetic susceptibility consumes **gluten**, which is found in wheat, barley, and rye. Gluten is composed of long protein fibers called glutenin and short amino acid polymers called gliadin. The antigenic molecule is **gliadin**. Gliadin gets into the lamina propria (we're not sure if it's M cells, enterocyte uptake, or intraepithelial migration, but it definitely gets past the basement membrane), where it encounters **tissue transglutaminase (tTG)**. tTG deamidates gliadin. Deamidated gliadin is picked up by resident macrophages (dendritic cells), which take it to the regional lymph node and display it to lymphocytes via MHC class 2. In those with the genetic susceptibility of the HLA-DQ2/DQ8 haplotype (this haplotype is neither necessary nor sufficient for the disease, but it is often present in those with the disease), this deamidated gliadin is identified as foreign. There are two outcomes. The first is that B cells differentiate to plasma cells and produce IgA and IgG antibodies (anti-gliadin, anti-tTG, anti-TG2, anti-endomysial). The second is the development of a **gluten-specific T_H1 population in the lamina propria**.

On re-exposure to gliadin, **enterocytes secrete IL-15**. Enterocytes use IL-15 to inform the IE-CTLs to get ready to kill enterocytes. IL-15 induces the expression of NKRs (technically decreased gene expression of *NKG2A* and increased gene expression of *NKG2D*, but sometimes others). IL-15 also inhibits Tregs, thereby effectively disinhibiting the gluten-specific T_H1 cells in the lamina propria. Those T_H1 cells express CD21 and IFN-γ. Both **CD21** and **IFN-γ** affect the IE-CTLs and enterocytes, causing the IE-CTLs to express more NKRs and enterocytes to express more NKR ligands. IE-CTLs bind more readily to enterocytes, inducing apoptosis. The result is the autoimmune destruction of the intestinal villi. This explains why celiac disease doesn't improve immediately after the withdrawal of gluten. First, the villi were lost in response to the gluten. Second, ongoing inflammation persists beyond the passage of gluten—the cells continue to do damage even though the gluten is no longer present in the lumen. Third, it takes time for the crypts to regenerate enough cells to restore the villi.

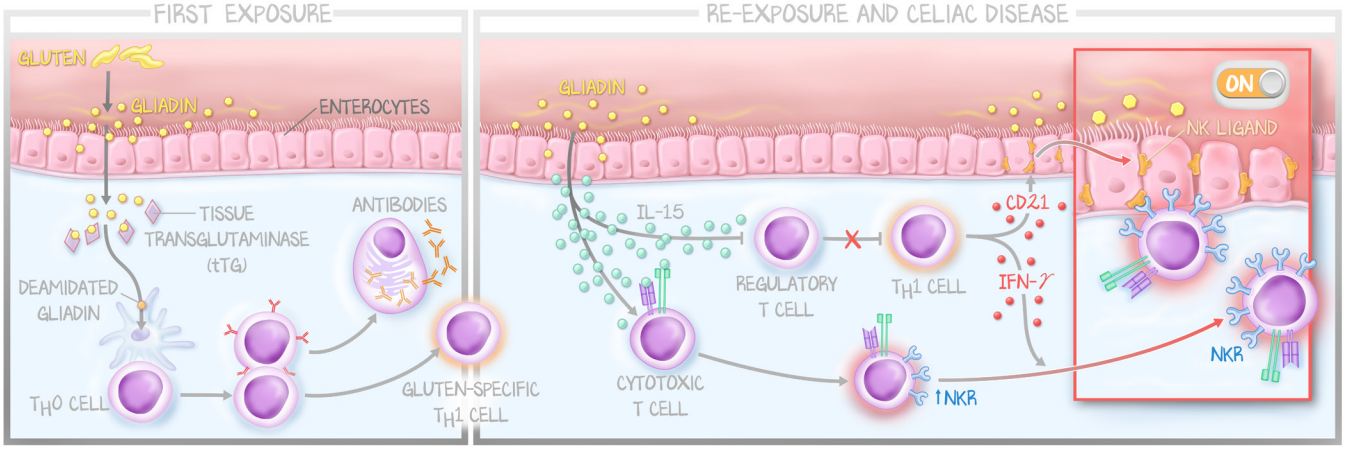

Figure 9.3: Celiac Disease
On first exposure, a dendritic cell (resident macrophage) takes deamidated gliadin, made from gliadin by tissue transglutaminase, to a naïve T_H0 cell in a nearby lymph node. In genetically susceptible patients, that T_H0 cell is activated into a gluten-specific T_H1 cell and induces plasma cells to express anti-gliadin IgA and IgG. Lymphocytes populate the lamina propria of the duodenum. On re-exposure, IL-15 is secreted by the enterocytes, inhibiting Tregs, which disinhibiting the gluten-specific T_H1 cells. IL-15 also activates intraepithelial cytotoxic T cells, which express NKRs. The disinhibition of gluten-specific T_H1 cells results in the expression of CD21 and IFN-γ, which increases the expression of NKR on T cells and NKR ligand on enterocytes, which then leads to tissue destruction through apoptosis and the loss of villi. In the illustration, we opted for the clarity of signaling and receptor-ligand interactions, so notice that the T cells' location is not intraepithelial, and technically, one is luminal and one in the lamina propria.

Testing should be done after 2 weeks of ingesting gluten to ensure that the immune response generates antibodies and the epithelium demonstrates pathologic changes. On biopsy (definitive diagnosis is made with endoscopy with biopsy), there is a **blunting of the intestinal villi** (the villi are not as tall as they should be, and the ratio of villus height to crypt depth greatly decreases) and **intraepithelial lymphocytosis** (more lymphocytes than usual above the basement membrane). There is also **crypt hyperplasia** (stem cells replicate from the crypt, trying to restore the villi). This is evidenced by increased mitosis in intermediate cells of the villus stalk.

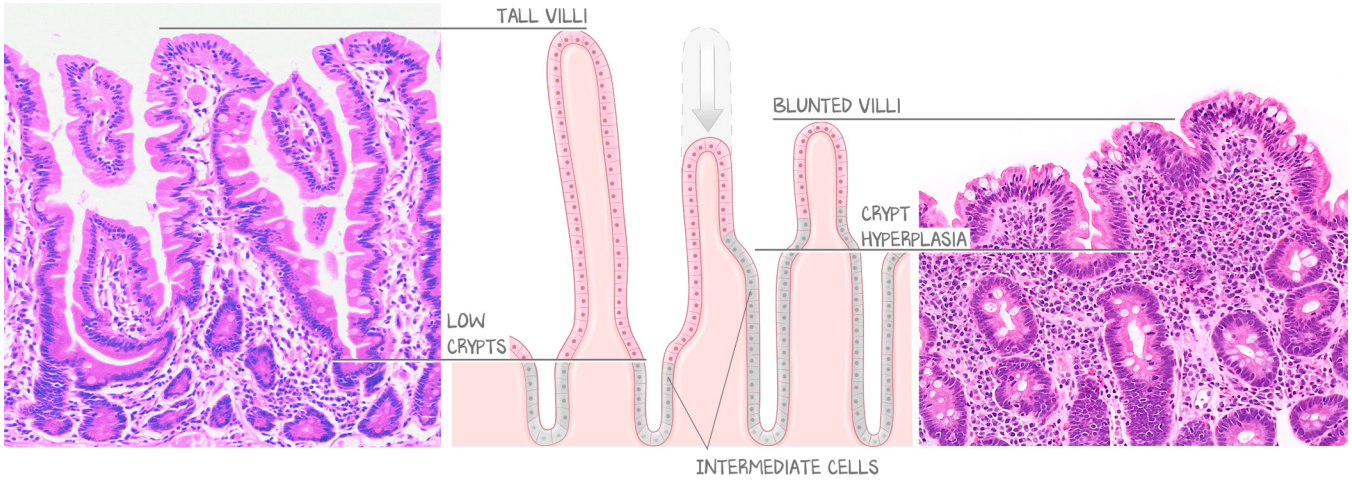

Figure 9.4: Celiac Histology
High-magnification view showing the histology of normal duodenal villi on the left. They are tall, slender, finger-like projections of the epithelium. The depth of the crypts is far lower. Contrast this appearance to that of the duodenal villi in celiac disease, shown in the image on the right. The illustration identifies what each histology is demonstrating—taller crypts because the cells of the crypts are intermediate cells, and celiac disease promotes increased proliferation to accommodate the loss of villi.

Avoidance of gluten will be completely curative. There is no treatment except **avoidance of gliadin**.

There are two patient presentations: infantile and adult. In the infantile form, fussiness, diarrhea, and **failure to thrive** (falling behind in height and weight for age) occur with the introduction of gliadin-containing foods. The adult form is harder to diagnose, with the symptoms being more vague, such as **chronic diarrhea** and **bloating**. Most diarrheal illness related to food improves after a day of abstinence. But because this is an autoimmune disease, it takes much longer, and gliadin avoidance for up to 3 months may be required for symptoms to abate. There is **duodenal inflammation**. This causes **carbohydrate malabsorption**, leading to loose, watery stool. Because the duodenum is affected, a **folate** or **iron deficiency anemia** may be provoked. Long-term consequences are **osteoporosis** as calcium is absorbed in the duodenum, and an increased incidence of **T cell lymphoma** and small bowel adenocarcinoma. Thus, if symptoms return after a dedicated gluten-free diet, suspect malignancy.

The pathognomonic feature is **dermatitis herpetiformis,** described in detail in Musculoskeletal: Dermatology #13: *Blistering Diseases*. Caused by the deposition of IgA antibody-antigen complexes in the dermal papillae, there is an eruption of vesicular lesions that are erythematous and intensely pruritic (they look like herpes but erupt in places herpes shouldn't).

Malabsorption Syndromes #2: Other Wheat Syndromes

Nonceliac gluten sensitivity (NCGS) is a yet-to-be-understood variant of gluten sensitivity. In NCGS, there are no antibodies, no villous blunting, and no crypt hyperplasia, even after weeks of gluten ingestion. It is a diagnosis of exclusion, specifically ruling out celiac disease. Most patients with NCGS self-diagnose and opt to eliminate gluten from their diet. Of those who do self-diagnose, two-thirds are unaware of any reintroduction of gluten into their diet, and their gluten-related symptoms hinge on their knowledge of the gluten's presence (i.e., they're psychosomatic). The remaining one-third of patients who self-diagnose NCGS have an obvious symptomatic change, even when gluten is introduced without their knowledge. The causative agent is thought to be another protein in the wheat kernel called fructan.

Wheat Allergy is a type 1 hypersensitivity reaction induced by the cross-linking of IgE, inducing mast-cell degranulation and histamine release, just like any other allergy. Some children develop allergies to peanuts, shellfish, and bee stings, and some develop allergies to wheat. It is treated the same as any other allergic reaction—avoid the allergen, and in the case of anaphylaxis, administer intermuscular epinephrine.

Malabsorption Syndromes #3: Select Few Remaining Syndromes

Tropical sprue is now called **environmental enteropathy**. We used to say, "*We don't know what causes it, but the biopsy looks like really bad celiac disease. Poor people in the Caribbean and India get it; treat with antibiotics*." This has changed. The new name is **environmental enteropathy**. It is indeed a disorder prevalent in areas with poor sanitation and hygiene, and often in impoverished communities in Brazil, India, Gambia, and Australia. There is **no causal organism identified**. Biopsies of the duodenum from patients with tropical sprue have revealed an appearance identical to that in severe celiac sprue (**loss/atrophy of villi**), but no antibodies or response to a gluten-free diet. There are presently no accepted clinical, laboratory, or histopathologic criteria that allow the diagnosis of environmental enteropathy. But whatever it is, it causes irreversible cognitive deficits, failure of oral vaccines, and the deaths of a whole bunch of poor kids. Licensure exam review materials still teach, *"ileum damaged more, so B_{12} deficiency. If celiac symptoms, but returned from tropics, it is tropical sprue."* That may mean that it comes up on the exam this way.

Whipple's disease. This barely exists in life—more than 90% of clinicians, including gastroenterologists, will never encounter this disease in a career of 40 years or more. However, it is a favorite of licensing

exams, honoring the pathologist who won the Nobel Prize for pernicious anemia and named this disease (not the surgeon who came up with the Whipple procedure). It occurs most commonly in Caucasian men, particularly farmers with occupational exposure to soil or animals. There are many healthy carriers, and so few presentations of this disease, that there is likely some genetic defect required as well as infection with the organism. But because the first case was so well described, we get to see it over and over again on exams. It is caused by an infection with ***Tropheryma whipplei***, an **intracellular** rod-shaped bacillus. Symptoms arise because **organism-laden macrophages** accumulate in the intestinal lamina propria and mesenteric nodes, causing a lymphatic obstruction. Lymphatics drain fats from the enterocytes. Obstruct the lacteals, obstruct the fat absorption, get **fat malabsorption**. The stool findings are **steatorrhea**, fat-soluble vitamin deficiencies, and weight loss. Infected macrophages also are found in joints and heart valves. The "classic" (the first patient exhibited this triad) findings are a triad of **diarrhea**, **weight loss**, and **arthralgia**. But the bug can affect literally any organ, even before malabsorption syndromes present themselves. On biopsy, there will be swollen **macrophages** in the lamina propria. They will **stain PAS-positive**. Under electron microscopy, there will be **intracellular organisms** within the macrophages.

The constellation of symptoms that constitutes Whipple's disease is similar to those of disseminated tuberculosis (which is way more common), which can be differentiated from Whipple's disease by an acid-fast stain. Whipple's disease **doesn't stain for acid-fast,** TB does. For Whipple's disease, look for a white farmer with arthralgia and steatorrhea. Little is known about this disease, and most people who have the bacteria are asymptomatic carriers.

Figure 9.5: Whipple's Disease
The first, low-magnification image shows multiple villi engorged and bloated with vacuolated spaces (white) where lipid used to be, removed during histological processing. The lamina propria is distended with lipid-laden macrophages (foam cells; not visible at this low magnification), resulting in stagnation of lacteal flow and fat malabsorption. With increasing magnification, abundant PAS-positive granules are seen in numerous macrophages, which fill the lamina propria. The simple columnar epithelium is intact and healthy, but the sheer number of macrophages distorts the villi and crypts. Each macrophage is separate from its neighbors but full of red granules, giving the appearance that there are red cells separated by white space. In truth, the white space represents the cytoplasm without granules. In the highest-magnification image, only a small number of cells are affected by the granules. You can see the discrete granules, and the solid red appearance is just because of the abundance of granules in a given cell.

Lactose intolerance. We covered this in the Biochemistry Metabolism module. If there is no lactase, the brush border **cannot digest lactose** (a disaccharide). Because it is a disaccharide, the brush border **cannot absorb lactose**, either. So, it is sent to the colon, where bacteria are very happy for their food.

The resultant bacterial fermentation of lactose results in bloating, gas, and diarrhea. Certain ethnicities (e.g., Asians) tend to have less lactase, but all infants can digest their mother's breastmilk, and therefore, humans begin life with lactase. Lactase is a "use it or lose it" enzyme, thus avoidance of lactose is enough to acquire lactase deficiency. Lactase enzyme replacement mitigates all the uncomfortable symptoms. However, its supplementation means that endogenous production will be further downregulated. For licensing exams, look out for stool studies of diarrhea. Lactose causes an **osmotic effect** and pulls water into the colon, resulting in watery diarrhea. Colonic bacteria ferment lactose, resulting in H^+ secretion, **reducing stool pH**. This diagnosis should not require endoscopy, but a tricksy question may show you a normal epithelium and ask you to know that enzymatic deficiency does not damage the epithelium. Unlike celiac disease, lactase deficiency improves days after dairy cessation or the initiation of lactase enzyme replacement. Another lactose intolerance-related topic common on licensures exams is the **hydrogen breath test**, where you feed someone lactose and then measure the H_2 produced in their breath. If they produce a lot of H_2, it's because of the H^+ made by the bacteria in their colon, and indicates a positive test result for lactase deficiency/lactose intolerance.

Citation

Figures 9.4a, 9.4b, 9.5a, Courtesy of WebPathology.

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